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| EXAMINER | |
|---|---|
| BRISTOL, LYNN ANNE | |
| ART UNIT | PAPER NUMBER |
| 1643 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/577,343 | NISHIMURA ET AL. | |
| | Examiner | Art Unit | |
| | LYNN BRISTOL | 1643 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *9-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

1. Claims 9-14 are all the pending claims in this application.

2. Claims 1-8 were cancelled and new Claims 9-14 were added in the Response of 11/20/09.

3. Claims 9-14 are all the claims under examination.

4. Applicants amendments to the claims have necessitated new grounds for rejection. This Office Action is final.

***Withdrawal of Rejections***

***Claim Rejections - 35 USC § 112, second paragraph***

5. The rejection of Claim 3 for omitting essential steps for measuring GPC3 either intracellular (also genomic DNA), extracellular or secreted and the means for measuring the GPC3 is moot for the cancelled claim.

6. The rejection of Claims 3-5, 7 and 8 for omitting the steps(s) comprising the control sample or GPC3 standard (e.g., protein, nucleic acid) against which any amount of GPC3 in the form of protein or nucleic acid is detected is moot for the cancelled.

***Claim Rejections - 35 USC § 112, first paragraph***

***Enablement***

7. The rejection of Claims 3-5, 7 and 8 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for practicing a

diagnostic method using any anti-GPC3 antibody directed to any epitope on the protein and in the absence additional art-recognized melanoma biomarkers is moot for the cancelled claims.

***Enablement***

8. The rejection of Claims 3, 5, and 8 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for a diagnosing risk for malignant melanoma based on quantitating the GPC3 mRNA or cDNA much less in the absence of quantitating another art-recognized melanoma marker and that would allow a risk assessment of the subject to melanoma is moot for the cancelled claims.

***New Grounds for Rejection***

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 9-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 9-14 are indefinite for failing to define the meaning of "a control value" against which the sample measurement is compared. Is this an ascertained amount of protein, mRNA or cDNA for GPC3? A control value can also be control amount of an irrelevant protein, mRNA or cDNA used in a standard curve, and against which the amount of test sample is quantified. Is a control value a normal skin cell or some normal

cell type equivalent for a malignant melanoma? The ordinary artisan could not determine the meets and bounds for practicing the method claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

***Written Description/ New Matter***

10. Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

a) Claims 12-14 are drawn to a GPC3 detection method where GPC3 mRNA or cDNA is detected in the body fluid for example a serum sample. The examiner's search of the specification for the limitation does not identify literal support for this limitation. (MPEP 706.03(m) states in part "New matter includes not only the addition of wholly unsupported subject matter, but may also include adding specific percentages or compounds after a broader original disclosure, or even the omission of a step from a method. See MPEP § 608.04 to § 608.04(c). See In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976) and MPEP § 2163.05 for guidance in determining whether the

addition of specific percentages or compounds after a broader original disclosure constitutes new matter.")

The specification (in the PGPub) teaches at [0042] "Moreover, when a body fluid such as a serum is used as a sample, the presence or the absence of the development of malignant melanoma can be determined by causing the sample to come into contact with the above antibody and then quantitatively detecting the specific binding between GPC3 (that can be present in the sample) and the antibody with the use of a fluorescent substance, a light-emitting substance, a secondary antibody, or the like, labeled with an enzyme or the like."

This is a new matter rejection.

***Enablement***

11. Claims 9-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting soluble or membrane associated GPC3 protein using an antibody recognizing an extracellular domain of the protein (e.g., 303-464) in a method for diagnosing (or at risk of having) malignant melanoma along with other clinically relevant melanoma tumor markers (e.g., 5-S-CD and MIA), does not reasonably provide enablement for practicing a diagnostic method using any anti-GPC3 antibody directed to any epitope on the protein and in the absence additional art-recognized melanoma biomarkers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/ Skill in the Art

The claims are interpreted as being drawn to a method for diagnosing a malignant melanoma comprising detecting or measuring GPC3 in a sample from a subject at risk of having the cancer, where the sample of Claim 3 is contacted with an anti-GPC3 antibody, or where the method of Claim 3 comprises quantifying GPC3 in a sample or where the antibody of comprises quantifying GPC3 in a sample and the sample is a body fluid or skin sample where the fluid is serum.

The relative skill required to practice the invention is a clinical diagnostician performing clinical histological diagnostic assays.

Disclosure in the Specification

The specification teaches and demonstrates detecting and quantifying GPC3 protein in histological sections from melanoma subjects (Example 4) and serum samples from malignant melanoma subjects (Example 5) using the commercially available antibody, 303-464.

For example, for histology, samples from melanoma, pigmented nevus and normal skin regions were compared using the immunohistology technique described in Nakatsura et al. (Biochem. Biophys. Res. Commun. 281, 936-944 (2001); cited in the IDS of 11/13/07). Figure 2 shows that GPC3 protein is highly expressed in 17/21 melanoma cases and 10/11 pigmented nevus cases (p. 16, Example 4), but the specification does not describe a positive/negative control marker and therefore, a control/standard would seemingly be required to distinguish a melanoma from a pigmented nevus.

For ELISA detection of GPC3 protein in sera from melanoma patients (Example 5; Figure 4), the 303-464 was used to coat plates and another commercial biotinylated rabbit polyclonal anti-GPC3 antibody was used to detect the protein in sera. For these studies, samples were obtained from patients' whose profiles were collected from medical records and then clinical stages were determined based on the TNM classification. The amounts of the GPC3 protein in sera was compared with the melanoma biomarkers, 5-S-CD and MIA, and correlated with melanoma staging from Stage 0-IV.

The ordinary artisan could not practice the method to reliably, reproducibly and predictably diagnose a subject suspected of being at risk for malignant melanoma absent the use of specific control reagents and control samples. The ordinary artisan would not have been enabled to practice the instant method at the time of the invention because the scope of the claims excludes several steps and reagents required to make a clinical immunoassay/histological diagnosis for melanoma. The Claims embrace

measurement of GPC3 protein by any method, either intracellular, extracellular or secreted and the means to measure GPC3 is not even defined.

The claimed antibodies against GPC3 are not clearly defined. It is clear from the specification that an antibody used in the working methods recognizes soluble parts/fragments of GPC3. Glypican 3 is however a membrane bound protein. Thus, only antibodies against secreted/soluble GPC3 can be used in the claimed method. The antibodies against GPC3 should be specified and they are not. The specification teaches that the detection of soluble forms of human GPC3 in serum samples of patients pre-diagnosed with melanoma is important for the present diagnostic method, i.e. to diagnose malignant melanoma in an early state compared to prior art diagnostic methods. However, the only biomarker considered in the entire diagnostic method is GPC3 and the ordinary artisan cannot even practice the instant claimed method without discriminating a melanoma from a heavily pigmented nevus. Thus the claims do not meet the how-to-practice requirement under the enablement analysis.

Prior Art Status: Immunohistology detection of melanoma requires standardization

Smith et al. (Vet. Pathol. 39:651-678 (2002); cited in the PTO 892 form of 8/25/09) teach prior to the invention filing date the immunohostology is a critical "ancillary diagnostic method" for differentiating amelanotic and poorly differentiated melanomas in animals including humans which often elude definitive diagnosis and neoplasms that mimic melanoma microscopically. Smith discusses the use of different biomarkers, for example, vimentin, S100, NSE but cautions that these markers can be

"found in a variety of tissues" non-specific for melanoma (p. 669, Col. 1, ¶2). Melan-A shows a narrow tissue distribution and has been studied in canine melanomas along with vimentin, S100, NSE expression. Smith states:

> "It remains unproven that Melan-A expression is a predictor of less aggressive behavior, but it may be a worthwhile marker for identification of tumors of uncertain lineage, especially when used in combination with S100" (p. 669, Col. 2, ¶2),

and

> "The advent of murine antibodies specific for melanoma-associated antigens, particularly melanosomes, has helped improve the value of IHC in the diagnosis of melanoma in human medicine. Often a panel of appropriate antibodies is advocated, an approach also favored in veterinary literature" (p. 670, Col. 1, ¶2),

and

> "IBF is the first murine monoclonal antibody specifically created to recognize canine melanoma antigen and is highly sensitive (greater than 80%). Although it does cross-react with other types of neoplasia, such as basal cell tumors and lymphosarcomas, these neoplasms can easily be ruled out using additional immunohistochemical testing and, on the whole, are not likely to be confused morphologically in the first instance (p. 679, Col. 1, ¶3).

Rutler et al. (Sem. Oncol. 29(4):370-381 (2002); cited in the PTO 892 form of 8/25/09) focused melanoma diagnostics for human patients relying on histopathological findings which AJCC-approved criteria for TNM classification and staging system of melanomas. Rutler teaches:

> "A large number of molecular-biologic and immunohistochemical studies have sought new prognostic markers that identify patients at risk for local recurrence or metastatic disease. However,

> most of these markers are merely a reflection of tumor progression and do not improve the classic prognostic model that is based on evaluation of thickness, level of invasion, mitotic rate, ulceration, regression, and vascular invasion on routinely stained tissue sections...[*but*] a few molecules identifiable with immunohistochemistry have been claimed to carry additional prognostic significance" (p. 374, Col. 2, ¶2),

and these markers include integrins, MMP-2, VEGF, Mitf, and CD40 (pp. 374-375).

The conclusion to be drawn from these reviews for diagnosing malignant melanoma is that careful, detailed controls including sample control tissues and other art-recognized biomarkers for melanoma having a clinical stage-correlation for melanoma are required to practice the method invention. The ordinary artisan could not have practiced the claimed invention in order to unequivocally diagnose malignant melanoma in any subject using only GPC3 expression as the sole biomarker indicia. The ordinary artisan would not have had a reasonable expectation of success based on the prior art references and where the only marker is GPC3 and the method is performed in the absence of relevant control samples. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

***Enablement***

12. Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting GPC3 mRNA in a solid tissue or cell sample from a melanoma patient, does not reasonably provide enablement for a diagnosing risk for malignant melanoma based on quantitating the GPC3 mRNA or cDNA much less in the absence of quantitating another art-recognized melanoma

marker and that would allow a risk assessment of the subject to melanoma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/ Skill in the Art

The claims are interpreted as being drawn to a method for diagnosing a malignant melanoma comprising detecting or measuring GPC3 mRNA or cDNA in a sample from a subject at risk of having the cancer where the method comprises quantifying GPC3 in a sample with a probe or a primer capable of detecting GPC3 expression and the sample is a body fluid or skin sample where the fluid is serum.

The relative skill required to practice the invention is a clinical diagnostician performing clinical molecular diagnostic assays.

Disclosure in the Specification

The specification teaches and demonstrates detecting and quantifying GPC3 expressed message in human melanoma cell lines (Example 2) and tissues from

malignant melanoma subjects (Example 3) using RT-PCR reaction according to Nakatsura et al. (Biochem. Biophys. Res. Commun. 281, 936-944 (2001); cited in the IDS of 11/13/07).

For human melanoma cell lines in Example 2, the GPC3 mRNA was detected using GPC3 PCR primers of SEQ ID NO: 3 and 4 and beta-actin primers as control standard. For human melanoma tissues in Example 3, GPC3 mRNA was compared in normal skin, human melanoma and human pigmented nevus tissues using the same primers. The specification does not describe a positive/negative control marker that distinguishes for example, a melanoma from a pigmented nevus, and therefore, a tissue-specific control/standard biomarker would seemingly be required to practice the method where measuring the control marker mRNA or cDNA is required for qualtitative and quantitative comparison.

The ordinary artisan could not practice the method to reliably, reproducibly and predictably diagnose a subject suspected of being at risk for malignant melanoma absent the use of specific molecular biological control reagents and control samples. The ordinary artisan would not have been enabled to practice the instant method at the time of the invention because the scope of the claims excludes several steps and reagents required to make a clinical molecular diagnosis for melanoma. The claims embrace measurement of GPC3 nucleic acid by any method and the means to measure GPC3 expression is not even defined. The specification teaches that the detection of GPC3 in tissue samples of patients pre-diagnosed with melanoma is important for the present diagnostic method, i.e. to diagnose malignant melanoma in an early state

compared to prior art diagnostic methods. However, the only biomarker considered in the entire diagnostic method is GPC3 and the ordinary artisan cannot even practice the instant claimed method without discriminating a melanoma from a heavily pigmented nevus using only the GPC3 mRNA transcript. The claims embrace any undisclosed probe or primer capable of detecting GPC3 message or cDNA in any sample yet the only primers disclosed as capable of being used in the RT-PCR are those of SEQ ID NOS: 3 and 4. The specification asserts common knowledge that RT-PCR can be used to detect the presence of a specific GPC3 mRNA population in a complex mixture of thousands of other mRNA species using the primers in Example 2 under the conditions described in Nakatsura without disclosing the cell or sample type. Thus the claims do not meet the how-to-practice requirement under the enablement analysis for the full scope of embodiments.

Prior Art Status: Quantitative Gene Amplification by RT-PCR is Unpredictable Without Normalization

The specification does not disclose or enable the reference genes used to practice the method in a manner that would allow the ordinary artisan to predict that the suject was at risk for having malignant melamoma. The specification does not disclose a control condition to specifically identify and quantitate an expression level for the GPC3 nucleotide sequence in any patient sample. The importance of RT-PCR standardization more especially in for clinical diagnostics where for routine optimization is required is highly unpredictable based on the prior art.

Bergkvist et al. (Genet. Engineer. News 28(13):26 and 28 (July 2008); cited in

the PTO 892 form of 8/25/09) specifically teach mRNA must be extracted and converted to cDNA by reverse transcription process and can produce a highly variable yield depending on the protocol. RNA is further rapidly degraded, and generally when assaying biological subjects, there is a need to minimize confounding technical and biological variability while maximizing the studies effect. Another caveat is the assay design (targeted sequence, the primers and the probe) which can give rise to a variation in the PCR efficiency among the studied genes, while any interfering substances inhibit PCR in a sample-dependent manner. The inset on p. 28 of Bergkvist identifies 8 variables that alone and in combination would reduce quantitative and qualitative assay efficiency.

Bustin et al. (Gen. Eng. News 29(14): 40-42 (8/1/09); cited in the PTO 892 form of 8/25/09) discuss the importance and challenges for systemitizing quantitative RT-PCR especially regarding consistency between laboratories, where as in the present case, the clinical diagnostician should be reasonably assured of being enabled to replicate the method from amongst different clinical laboratories. Bustin states that "the MIQE guidelines stipulate full disclosure of reagents, protocols and analysis methods thus establishing that qPCR data meets a minimal set of standards. This increases confidence in its validity by ensuring that data meets a uniform quality benchmark..."; and Bustin appreciates for RT-qPCR, RNA quality can vary and that normalizing RT-qPCR results to reference genes without knowledge of the degradation status of the RNA could lead to incorrect conclusions.

The specification provides incomplete working examples which would provide

guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention as currently claimed would function as claimed, in the absence of a controlled RT-PCR reaction condition, with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

Prior Art Status: Quantitative Hybridization Using Array Technology is Unpredictable

Claims 12-14 encompass the method of detecting GPC3 by a probe or primer in a microassay format where hybridization of GPC3 mRNA or cDNA to probes or primers arrayed on a solid support (e.g., gridding) in order to detect the presence of and to quantitate the level of gene expression. The specification does not so much as disclose a hybridization condition or a working example demonstrating quantitative hybridization in an array method. Liang et al. (Funct. Integr. Genomics 6:1-13 (2006); cited in the PTO 892 form of 8/25/09) specifically teach that microarray results differ substantially among replicates and requires replication to increase the validity (p. 3, Col. 1, ¶1) and that the expression of a large number of irrelevant and redundant genes, the high level of noise in measurements and uncertainties in the data severely degrade both classification and prediction accuracy which require gene filtering and differentiation approaches to highlight the most relevant genes (p. 3, Col. 2, ¶2). Preston (Environ. Molec. Mutagenesis 45:214-221 (2005); cited in the PTO 892 form of 8/25/09) teaches "it is currently quite difficult to use microarray techniques to obtain quantitative assessments of gene expression; this is the result of the relatively nonquantitative

nature of a number of steps in the process from total sample mRNA isolation and cDNA production to hybridization and detection. In addition, the method only detects transcripts that are relatively abundant in the cell. Thus microarray analysis is a useful tool for an initial survey of possible genes whose expression is altered, for example, by a chemical carcinogen…Additional RNA-based methods, such as real-time PCR or differential display, can be used to establish quantitative comparisons of expression among treatments, tissues, or organs for those genes identified as being interesting based on microarray analysis" (p. 217, Col. 1, ¶2 to Col. 1, ¶1).

The specification provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention as currently claimed would function as claimed, in the absence of a working example using a microarray, with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

***Enablement***

13. Claims 12-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting GPC3 mRNA in a solid tissue or cell sample from a melanoma patient, does not reasonably provide enablement for a detecting GPC3 mRNA in any sample including any fluid sample from a melanoma patient. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to use the invention as claimed.

Nature of the Invention/ Skill in the Art

The claims are interpreted as being drawn to a method for diagnosing a malignant melanoma comprising detecting or measuring GPC3 mRNA in any sample much less a fluid sample from a subject at risk of having the cancer where the method comprises quantifying GPC3 in a sample with a probe or a primer capable of detecting GPC3 mRNA expression and the sample is a body fluid or skin sample where the fluid is serum.

The relative skill required to practice the invention is a clinical diagnostician performing clinical molecular diagnostic assays.

Disclosure in the Specification

The specification demonstrates measuring GPC3 mRNA in samples obtained from human tissues and mouse and human cells in Northern blot assays. The specification does not teach how intact mRNA for GPC3 could be obtained from any

fluid much less serum without risk of enzymatic degradation by endogenous RNAses within the patient. The specification does not teach that GPC3 mRNA within any fluid much less serum would provide the measurable mRNA for the assay. Unless the mRNA were associated within a circulating, colonizing or metastatic tumor cell, then not all biological fluid samples could be used to detect the intact mRNA. Thus, the specification does not describe how one of ordinary skill in the art could obtain any one biological samples from a cancer patient and expect to find a non-degraded mRNA for the GPC3 in the sample.

Prior Art: Endogenous eukaryotic RNases and Isolation of mRNA

Meyer et al. (Clin. Rev. Biochem. & Molec. Biol. 39:197-216 (2004)) describe the properties of mRNA degradation within cells as being important for reaching steady state levels of protein expression. Meyer explains intracellular regulatory processes for mRNA degradation and that certain mRNA are more stable than others depending on signaling. Busesa et al. (J. Neuropathol. Exp. Neurol. 63(10):1003-1014 (2004); Abstract) teach the importance of decreasing mRNA degradation in brain biopsy tissues where hybridization techniques are used to examine profiling. At the time of the application, it was well recognized that mRNA stability was highly regulated within a cell, and that exposed or naked mRNA was highly susceptible to degradation absent the use of appropriate inhibitions or preservation techniques.

In view of the lack of predictability of the art for isolating full length mRNA from any biological sample, the art recognized presence of RNases in viable and post-mortem tissues, undue experimentation would be required to practice the claimed

methods with a reasonable expectation of success using blood, urine, interstitial fluid or ascites fluid as biological sample material, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for identifying an mRNA transcript encoding the amino acid sequence shown in SEQ ID NO:195, commensurate in scope with the claimed invention."

***Conclusion***

14. No claims are allowed.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Primary Examiner, Art Unit 1643